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MICROVASCULAR RECONSTRUCTION IN EXTREMITY SOFT TISSUE SARCOMA SURGERY

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ACADEMIC DISSERTATION

To be publicly discussed,
with the permission of the Faculty of Medicine of the University of Helsinki,
in the auditorium of Töölö Hospital, Helsinki University Central Hospital,
on November 19th at 12 noon.

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To all my teachers

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1. LIST OF ORIGINAL PUBLICATIONS

The thesis is based on the following original publications. These are referred to in the text by their Roman numerals.

I Popov P, Barner-Rasmussen I, Tukiainen E. Microvascular flaps and collateral ligament reconstructions for soft tissue sarcomas at the knee joint. Ann Plast Surg 2010; 64:24-7.

II Barner-Rasmussen I, Popov P, Böhling T, Tarkkanen M, Sampo M, Tukiainen E. Microvascular reconstruction after resection of soft tissue sarcoma of the leg. Br J Surg 2009; 96:482-9.

III Barner-Rasmussen I, Popov P, Blomqvist C, Tukiainen E. Microvascular reconstructions after extensive soft tissue sarcoma resections in the upper limb. Eur J Surg Oncol 2010; 36:78-83.

IV Tukiainen E, Barner-Rasmussen I, Popov P, Kaarela O. Forequarter amputation for malignancy: a report of 25 patients with a review of the literature. Submitted.

2. ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ALT	anterolateral thigh
ASA	American Society of Anesthesiologists
CT	computed tomography
DFS	disease-free survival
DFSP	dermatofibrosarcoma protuberans
DSOS	disease-specific overall survival
EBRT	external beam radiotherapy
FDG	^{18}F-fluorodeoxyglucose
FLT	^{18}F-fluorothymidine
FNCLCC	Fédération Nationale des Centres Lutte Contre le Cancer
FQA	forequarter amputation
GIST	gastrointestinal stromal tumor
HUCH	Helsinki University Central Hospital
ILP	isolated limb perfusion
LD	latissimus dorsi
LRFS	local recurrence-free survival
MDACC	M.D. Anderson Cancer Center
MFH	malignant fibrous histiocytoma
MFS	metastasis-free survival
MPNST	malignant peripheral nerve sheath tumor
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
MSTS	Musculoskeletal Tumor Society
NOS	not otherwise specified
OS	overall survival
OUH	Oulu University Hospital
PET	positron emission tomography
PLP	phantom limb pain
RT	radiotherapy
SSG	Scandinavian Sarcoma Group
SSS	surgical staging system
STS	soft tissue sarcoma
TAP	thoracodorsal artery perforator
TESS	Toronto extremity salvage score
TFL	tensor fasciae latae
TNF	tumor necrosis factor
UICC	Unio Internationalis Contre Cancrum

3. ABSTRACT

Background

Soft tissue sarcomas (STS) are rare tumors of soft tissue occurring most frequently in the extremities. Modern treatment of extremity STS is based on limb-sparing surgery combined with radiotherapy (RT), with other oncological treatment used less frequently. In order to prevent local recurrence, a healthy tissue margin of 2.5 cm around the resected tumor is required. This results in large defects of soft tissue and bone, necessitating the use of reconstructive surgery to achieve wound closure, especially in the distal parts of the extremities where soft tissues are scarce. When local or pedicled soft tissue flaps are unavailable or insufficient, reconstruction with free flaps is used. The free flaps are elevated at a distant site, and have their blood flow restored at the recipient site through microvascular anastomosis. When limb-sparing surgery is made impossible by tumor location or infiltration into vital structures, amputation is the only option. Proximal amputation such as forequarter amputation (FQA) causes considerable morbidity, but is nevertheless warranted for carefully selected patients for cure or palliation.

Materials and Methods

116 patients treated in 1985 - 2006 were included in the study. 73 patients treated with microvascular reconstructive surgery after resection of STS or related tumors of the lower extremity. 15 of these patients were treated for STS near the knee. 20 patients underwent microsurgical reconstructive surgery for STS or related tumors of the upper extremity. 25 patients who underwent forequarter amputation for STS or other malignant disease at Helsinki University Central Hospital (HUCH) or Oulu University Hospital (OUH) were also included. Patients were identified and their medical records retrospectively reviewed for data on demographics, tumor characteristics, treatment, and surgical, oncological and functional outcome. In all, 105 free flap procedures were performed for 103 patients. A total of 95 curatively treated STS patients were included in survival analysis.

Results

The latissimus dorsi, used in 56% of cases, was the most frequently used free flap. Free flap success rate was 96%. There were 9% microvascular anastomosis complications and 15% wound complications. For curatively treated STS patients, local recurrence-free survival at 5 years was 73.1%, metastasis-free survival 58.3%, disease-free survival 50.1% and overall disease-specific survival 68.9%. Functional results were good, with 75% of patients regaining normal or near-normal function after lower extremity, and 55% after upper extremity STS resection. Among 25 forequarter amputees, there was no perioperative mortality, and 5-year disease-free survival was 44% among curatively treated patients. In the palliatively treated group median time until disease death was 14 months.

Conclusions

Microvascular reconstruction after extremity soft tissue sarcoma resection is a safe and reliable method. Tension-free wound closure and cavity filling produces stable, well-healing wounds, allowing early oncological treatment. Oncological outcome after these procedures is comparable to that of other extremity sarcoma patients. Functional results are generally good. Forequarter amputation is a useful treatment option for soft tissue tumors of the shoulder girdle and proximal upper extremity and is associated with low operative morbidity. Acceptable oncological outcome is achieved for curatively treated FQA patients. In the palliatively treated patient increased quality of life can be achieved for considerable periods of time. When free flap coverage of extended forequarter amputation is required, the preferable flap is a fillet flap from the amputated extremity.

4. INTRODUCTION

Soft tissue sarcomas (STS) are rare tumors originating mainly from the embryonic mesoderm, the majority arising in the extremities (Pollock et al 1996; Nijhuis et al 1999). STS comprises less than 1% of all adult malignancies in Finland, with approximately 120 new cases diagnosed annually (Finnish Cancer Registry 2007).

Due to high rates of local recurrence after simple tumor excision, amputation used to be the treatment of choice for STS of an extremity (Cantin et al 1968). Combination of surgery and radiotherapy (RT) proved to achieve equal oncologic results with considerably less invalidity (Rosenberg et al 1982; Yang et al 1998). Limb-sparing treatment protocols combining surgery, radiotherapy and chemotherapy have since become the gold standard in the treatment of extremity STS (Clark et al 2005, Tunn et al 2009).

Oncologically safe resection of STS requires a healthy tissue margin of 1.5-2.5 centimeters (Pisters et al 1996 (B), Sampo et al 2008). Extensive soft tissue and bone defects are frequently caused. To enable limb sparing and to achieve satisfactory functional and cosmetic results, reconstructive surgery is required in 25-48% of patients (Popov et al 2000, Clarkson et al 2004, Popov et al 2004). Free flap reconstruction is necessary in 11-18% of patients (Lohman et al 2002, Kim et al 2004 (A), Papadopoulos et al 2006).

Today, amputation for extremity STS is uncommon, but in 9-13% of patients it is still unavoidable (Pisters et al 1996 (B), Trovik et al 2001 (A), Trovik 2001 (B)). In patients with shoulder girdle or proximal upper extremity tumors, forequarter amputation (FQA) can provide an option when limb sparing proves impossible (Malawer et al 2001).

The aim of this study was to review the use of free flaps in extremity STS surgery, and to evaluate factors affecting surgical and oncologic outcome.

5. REVIEW OF THE LITERATURE

5.1 Soft tissue sarcoma

Soft tissue sarcomas (STS) are a heterogeneous group of tumors arising mainly from mesenchymal tissues. The most common anatomical sites are lower extremity (29-49%), upper extremity (12-21%), retroperitoneum (8-15%), head and neck (4-13%), abdomen (10-12%), pelvis (7-12%), and thorax (9-11%) (Pollock et al 1996, Nijhuis et al 1999, Weiss et al 2001, Lohman et al 2002, Zagars et al 2003 (A), Cormier et al 2004, Kim et al 2004 (A), Gutierrez et al 2007 (A)).

5.1.1 Incidence

The incidence of soft tissue malignancies (ICD-10 codes C48-49) has been relatively constant, with approximately 2.0 new cases per 100 000 inhabitant-years. This figure excludes tumors of the autonomous nervous system and peripheral nerves (ICD-10 codes C47). With these included, incidence in 2000-2005 was 2.4/100 000, accounting for 0.9% of all adult cancers (Finnish Cancer Registry 2007).

In the US one study found 3.8 cases per 100 000 inhabitant-years in 2003, (Gutierrez et al 2007 (A)). Another study states that STS accounts for 0.63% of new cancer diagnoses and 1.15% of all cancer deaths (Jemal et al 2004). Signs of a slight increase in the overall incidence of STS has been explained by both improved recognition and diagnostics (Ross et al 1993, Clark et al 2005), as well as by the increased number of AIDS-related Kaposi's sarcomas (Zahm et al 1997).

5.1.2 Etiology

The majority of STS are considered to be sporadic, i.e. no specific etiological factors can be identified (Lahat et al 2008 (B)). Several factors that may cause

STS have, however, been recognized. Radiation therapy increases the risk of both bone and soft tissue sarcoma (Brady et al 1992, Virtanen et al 2006). Chronic lymphedema may cause cutaneous lymphangiosarcoma (Grobmyer et al 2000). Angiosarcoma arising from chronic lymphedema after mastectomy and radiotherapy is known as Stewart-Treves syndrome (Stewart et al 1943).

Environmental agents such as vinyl chloride, phenoxyacetic acid herbicides, and chlorophenols and their contaminants have been shown to increase the risk of sarcoma (Froehner et al 2001).

Certain genetic conditions are associated with STS. These include neurofibromatosis I (caused by a mutation in 17q11), which causes multiple benign neurofibromas in the patient, 1-5% of which will present as aggressive malignant peripheral nerve sheath tumors (MPNST) (Evans et al 2002, Ferrari et al 2007). Mutations of the tumor suppressor gene p53 causes Li-Fraumeni syndrome, associated with a wide range of malignancies, including STS (Gonzales et al 2009). Familiar retinoblastoma, caused by mutations in the retinoblastoma gene RB I (Wong et al 1997), also increases risk of sarcoma. The phenotypical variant of familial adenomatous polyposis (FAP) known as Gardner's syndrome is associated with increased risk of several neoplastic lesions, desmoid tumor among them (Lyster Knudsen et al 2001, Nieuwenhuis et al 2008). In Maffucci syndrome, benign enchondromas, hemangiomas and lymphangiomas may undergo transformation into their malignant sarcomatous counterparts (Albregts et al 1995).

Also, some viral agents increasing the risk of STS have been identified. Human herpesvirus 8 (HHV 8) plays a role in the development of Kaposi's sarcoma (Boshoff et al 2002, Sullivan et al 2008). Further, Epstein-Barr virus (EBV) infection has been found to cause leiomyosarcoma both in immunodeficient AIDS-patients (McClain et al 1995) and in organ-transplant recipients during therapeutic immunosuppression (Nur et al 2007).

5.1.3 Classification and histopathology

Soft tissue sarcomas generally present as a painless mass, and histological confirmation of diagnosis is crucial before treatment. Core-needle biopsy (CNB) provides the correct diagnosis in 90% of cases, whereas fine-needle aspiration (FNA) may produce insufficient amounts of tissue (Barth et al 1992, Hoeber et al 2001, Jones et al 2002). Infrequently, when tumor location is such that needle biopsy is not feasible, or when earlier biopsies have turned out inconclusive, incisional or open biopsy is warranted (Misra et al 2009). Care should be taken to place all incisions and biopsy tracts so that they can be easily excised en-bloc with sufficient healthy tissue margins with the biopsied tumor (Springfield et al 1996, Leithner et al 2009). The rarity and heterogeneity of these tumors makes diagnosis difficult, and histopathologic examination should preferably be carried out by an experienced soft tissue tumor pathologist (Clark et al 2005, Palesty et al 2005, Bjerkehagen et al 2009).

The World Health Organization Classification of Tumors now recognizes more than 50 distinct subtypes (Fletcher et al 2002). Undifferentiated pleomorphic sarcoma, previously known as malignant fibrous histiocytoma (MFH), is the most common type in adults, representing 28-39% of all STS. Liposarcoma (14-22%), synovial sarcoma (11-12%), leiomyosarcoma (6-12%), fibrosarcoma (8-9%) and MPNST (6-7%), are also among the more common subtypes in several large series. (Zagars et al 2003 (A), Cormier et al 2004, Mankin et al 2005, Gadgeel et al 2009). Among 1261 patients with extremity STS, Weitz reported MFH (38%), liposarcoma (27%), synovial sarcoma (14%) fibrosarcoma (12%) and leiomyosarcoma (9%) to be the most common histologic findings (Weitz et al 2003). Gutierrez reported similar findings in 4205 surgically treated STS patients: 54% MFH, 34% liposarcoma, 10% fibrosarcoma, and 1% other or unspecified histology (Gutierrez et al 2007 (A)).

The most prevalent subtype of STS is dependent on patient age, with MFH generally a disease of patients over 50 (Weiss et al 2001). Rhabdomyosarcoma

is by far the most common histologic finding in children, constituting more than 50% of pediatric STS (Cormier et al 2004, Hayes-Jordan et al 2009).

Histologic analysis supplemented by immunohistochemical analysis (Miettinen 2003) and genetic profiling (Segal et al 2003, Mandahl et al 2004) has increased diagnostic accuracy as many subgroups of STS have been shown to exhibit specific chromosomal changes (Brennan 2005).

5.1.4 Grading

In order to anticipate patient prognosis, tumors are graded for histological aggressiveness. The first grading system for STS was introduced by Broders in 1939, as a continuation on his work on squamous cell carcinoma (Broders 1920, Broders et al 1939). This 4-tiered system was based on mitotic activity, number of giant cells, and percentage of fibrous stroma in fibrosarcomas. Grades 1-2 (G1-G2) were regarded as low grade, and 3-4 (G3-G4) as high grade tumors. A 4-tiered system largely based on Broders' classification is used by the Scandinavian Sarcoma Group (SSG), and is also used in Finland (Angervall et al 1993). Also the 6th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) staging system uses a 4-tiered system based on cellular differentiation (Greene et al 2002).

Other grading systems were developed in the 80s; the 3-tiered system of the French Federation of Cancer Centers (FNCLCC) is based on cellular differentiation, mitotic rate, and tumor necrosis (Trojani et al 1984), whereas the 3-tiered National Cancer Institute (NCI) system on histologic diagnosis, cellularity, cellular pleomorphism, and mitotic rate (Costa et al 1984). Both 3-tiered systems use grade 1 (G1) for low grade, and grades 2-3 (G2-3) for high grade tumors. The most common system in use, and also the most reproducible, is the FNCLCC system (Guillou et al 1997, Golouh et al 2001). For clinical use, division into high or low grade is frequently the most practical, and a 2-tiered system has been proposed (Deyrup et al 2006, Kotilingam et al 2006).

5.1.5 Staging

Histological grade alone is not the only determinant of outcome. Staging systems use a variety of other factors to predict prognosis.

The Musculoskeletal Tumor Society (MSTS) staging system, also known as the Surgical Staging System (SSS), is based on 3 variables (Enneking et al 1980, Wolf et al 1996). The first is malignancy grade, determined histologically by cytologic atypia and mitotic activity, defining tumors as either low-grade (G1) or high-grade (G2). Secondly, a difference is made between intracompartmental (T1) and extracompartmental (T2). Intracompartmental tumors are confined to a specific anatomical compartment, whereas extracompartmental tumors infiltrate the borders of, or extend beyond these compartments. Thirdly, the last division is based on the absence (M0) or presence (M1) of metastasis. The final 3-tiered staging is based on these factors (Table 1).

TABLE 1. Surgical Staging System (SSS) of soft tissue sarcoma

Stage	Description	Grade	Site	Metastasis
IA	Low grade, intracompartmental	G1	T1	M0
IB	Low grade, extracompartmental	G1	T2	M0
IIA	High grade, intracompartmental	G2	T1	M0
IIB	High grade, extracompartmental	G2	T2	M0
III	Any grade, metastatic	G1-2	T1-2	M1

From Wolf et al 1996

Another staging system, incorporating tumor size, site, and histologic grade as three prognostic factors, was developed at Memorial Sloan Kettering Cancer Center (MSKCC). Each of these factors is divided into two subcategories, favorable and unfavorable prognostic signs. The number of unfavorable signs then determines STS stages 0-III. Metastatic disease is always stage IV (Tables 2 - 3) (Hajdu 1979, Hajdu et al 1988).

TABLE 2. Prognostic signs of the MSKCC staging system

	Favorable prognostic signs	Unfavorable prognostic signs
Size (≤5cm/>5cm)	Small	Large
Site (relative to deep fascia)	Superficial	Deep
Histologic grade	Low	High

From Hajdu et al 1988

TABLE 3. MSKCC staging system

Prognostic signs	Stage of sarcoma
Three favorable signs	0
One unfavorable signs and 2 favorable signs	I
Two unfavorable signs and 1 favorable sign	II
Three unfavorable signs	III
Evidence of metastasis	IV

From Hajdu et al 1988

The current 6th edition of the AJCC/UICC system is the most commonly used staging system (Kotilingam et al 2006). It incorporates tumor grade and size, as well as presence or absence of nodal (N0-N1) and distant metastases (M0-M1) (Table 4, Table 5) (Greene et al 2002).

Wunder et al compared the above staging systems, and found the 5th edition of the AJCC/UICC system to be as accurate as the MSKCC system in predicting systemic disease relapse in patients with localized extremity STS, whereas the SSS was inferior to these (Wunder et al 2000).

Accurate prediction of prognosis for STS patients has proven difficult. Even the latest staging systems have been criticized for not incorporating enough factors, among other things (Lahat et al 2008 (A)). An attempt towards better prediction of outcome has been made in the form of nomograms, notably one developed at MSKCC (Kattan et al 2002). It takes into account tumor size, depth and histology as well as anatomical site and patient age, and a 2005 variation of it also incorporates 3-tiered tumor grade according to FNCLCC grading (Mariani et al 2005).

TABLE 4. AJCC TNM classification

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor ≤ 5cm
T1a	Superficial tumor
T1b	Deep tumor
T2	Tumor > 5cm
T2a	Superficial tumor
T2b	Deep tumor
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
MX	Metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Histologic grade (G)	
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Poorly differentiated or undifferentiated

From Greene et al 2002

TABLE 5. AJCC TNM classification

Stage	Tumor (T)	Node (N)	Metastasis (M)	Grade (G)	Description
I	T1a, T1b, T2a, T2b	N0	M0	G1-2	Low grade
II	T1a, T1b, T2a	N0	M0	G3-4	Small high grade, or large superficial high grade
III	T2b	N0	M0	G3-4	Large deep high grade
IV	Any T	N1	M0	Any G	Lymph node metastasis
	Any T	N0	M1	Any G	Distant metastasis

Modified from Greene et al 2002

5.1.6 Surgical margins

Enneking defined surgical margins according to the width of healthy tissue around the resected tumor. He divided margins into radical, wide, marginal or intralesional groups. In radical excision, the entire compartment containing an

intracompartmental tumor is removed. Wide margin entails intracompartmental resection, with a cuff of normal tissue surrounding the tumor. Resection is considered marginal when the plane of dissection is within the reactive zone or pseudocapsule of the tumor. In intralesional resection there is tumor at the edge of the specimen (Enneking et al 1980). Another classification of surgical margins is used by the UICC, using the three categories R0-R2, where R0 equals no residual disease, R1 microscopic residual disease, and R2 macroscopic residual disease (Sobin et al 2002).

McKee et al demonstrated that margins of <1mm and 1-10 mm had significant, and equal, negative prognostic value for local recurrence (58% LRFS in both groups, compared to 84% for margins >1cm) (McKee et al 2004). A recent HUCH analysis of 270 patients with localized STS of the trunk wall or extremities showed that to achieve 5-year local-recurrence free survival rates of 90%, microscopic healthy tissue margin must be at least 2.5 cm (Sampo et al 2008). Dickinson et al had no local recurrences in patients with margin >20mm, but there were only 12 patients in this group. The authors concluded that 1mm margins may be safe, but that narrow margins increase the risk of inadvertent contamination (Dickinson et al 2006).

It has been convincingly demonstrated that positive surgical margins are a negative prognostic factor for all oncological endpoints (Pisters et al 1996 (B), Stojadinovic et al 2002, Zagars et al 2003 (A)). The required margin and the quality of healthy tissue separating the tumor from the edge of the specimen continue, however, to be an issue of debate. A recent review article states that the axiom of 2-3 cm margins is not scientifically proven, but is still used in many centers despite the increased need for ablative procedures when using a 2-3 cm margin instead of 1 cm (Tunn et al 2009). Another unanswered question regards the quality of the tissue margin required. According to Enneking's compartmental philosophy an intact fascia is sufficient margin, and a report on 50 patients with localized, large, high grade lower extremity STS from MDACC indicates that also periosteum is a sufficient barrier (Lin et al 2007).

5.1.7 Imaging

Radiological imaging is required to appropriately assess and stage STS, and to plan surgical and oncological treatment. Goals are to evaluate the location, size, homogeneity, and possible calcification of the tumor. Relationship to, or infiltration into, nearby vital structures such as nerves or blood vessels is of paramount importance for treatment planning.

Radiographs of the suspected STS have historically been the first-line imaging method. In addition to being inexpensive and readily available, involvement of underlying bone can be assessed. Also, certain typical findings of specific diagnoses (such as phleboliths of hemangiomas) can be identified in plain radiographs (Knapp et al 2005).

The main imaging modality for extremity STS is MRI. High-quality morphological images, multi-plane imaging capability, and lack of ionizing radiation load make it the preferred technique for detection, delineation, differential diagnostics, and monitoring response to treatment, as well as for postoperative follow-up. It is also used for needle-biopsy guidance (Demas et al 1988, Knapp et al 2005, Palesty et al 2005, Tzeng et al 2007, Robinson et al 2008). Its accuracy in evaluating fascial involvement and relationship of a tumor to adjacent structures allows detailed operative planning (Figure 1) (Clarkson et al 2004, Hünerbein et al 2007).

For imaging the trunk and intra-abdominal STS, and for evaluation of bone involvement, CT is preferred (Fenstermacher et al 2003, Misra et al 2009). CT is also the imaging of choice for patients that cannot undergo MRI (Tzeng et al 2007).

Ultrasonography is readily available and cheap, and can sometimes be of use for distinction between solid and cystic masses (synovial cyst, bursa, abscess) (Lin et al 2000, Knapp et al 2005). It’s perhaps most important application in STS diagnostics is for needle biopsy guidance (Misra et al 2009). Magnetic

resonance angiography gives detailed information about vascular supply of tumors, and can also be of use in vascular lesions (Knapp et al 2005).

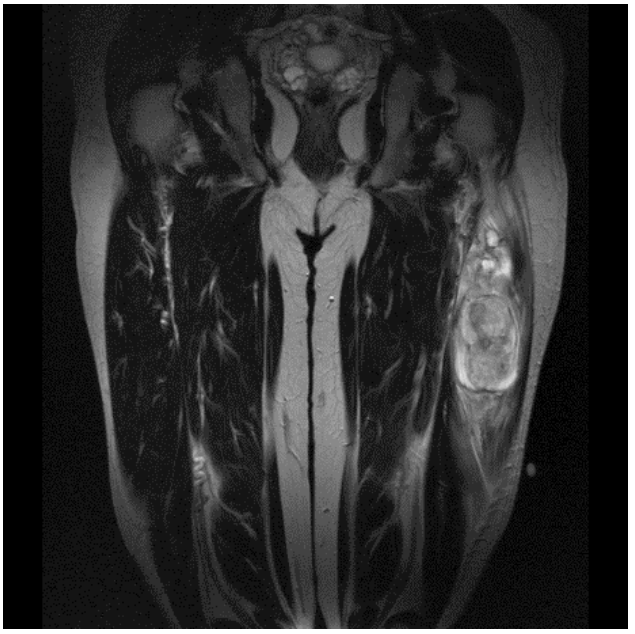

FIGURE 1. MRI image of an intramuscular grade 4 MFH of the thigh.

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has emerged as a new tool in STS imaging (Schuetze et al 2006). FDG allows visualization of tissue glucose metabolism activity. Functional imaging by PET can be used for STS detection, differential diagnostics, biopsy guidance, for distinguishing between recurrences and therapy-related changes, and for monitoring of response to treatment (Buck et al 2008, Evilevitch et al 2008, Toner et al 2008). PET, especially in combination with CT, has proven useful in preoperative TNM-staging (Iagaru et al 2006, Tateishi et al 2009). ^{18}F-fluorothymidine (FLT) has been studied in assessment of tumor cell proliferation, but is still mainly in experimental use (Benz et al 2009)

There has been some discussion on whether plain chest radiographs should be performed for all STS patients for staging as most STS metastases are found in the lungs. Some recommend a chest CT scan for all patients as the primary modality (Misra et al 2009), whereas others advocate selective use of

modalities, with primary CT recommended for >5cm high grade (AJCC T2) lesions only (Robinson et al 2008). A review of 1170 patients found 10% metastatic disease at presentation, of which 87% were lung metastases. Plain chest radiographs identified 2/3 of these, and the authors conclude by recommending chest radiographs for all patients, and primary CT only for patients with an abnormality in these. In addition, chest CT is recommended for patients with large, deep, or FNCLCC grade 2-3 tumors, and other biologically aggressive histological subtypes (including extraskeletal Ewing sarcoma and MPNST) (Christie-Large et al 2008).

5.1.8 Natural history and survival

STS frequently present as a painless mass (Figure 2), and has a tendency to grow for long periods of time within an anatomical compartment and along fascial planes (Robinson et al 2008). The growing mass compresses the surrounding tissues, creating a pseudocapsule around the tumor. The tumor

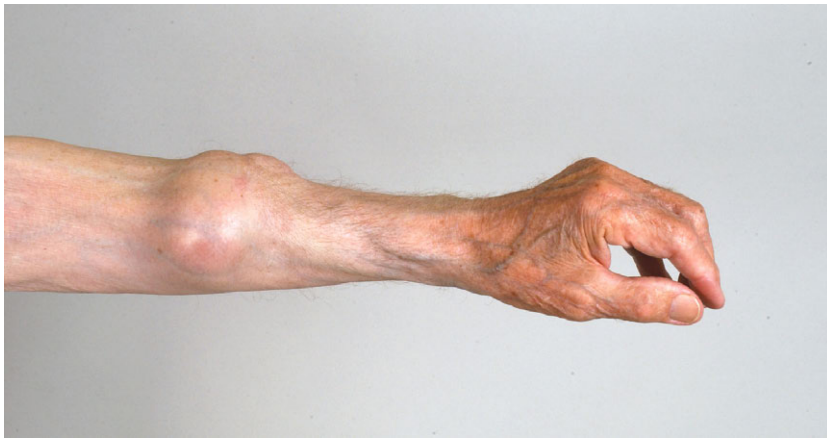

FIGURE 2. A primary 4.5 cm extracompartmental grade 4 MFH of the forearm.

itself, however, frequently extends into the reactive zone surrounding the pseudocapsule, and simple “shellout” procedures result in local failure in up to 90% of patients (Weiss et al 2001).

The most common site for STS metastasis is the lung, with 19-20% of patients developing pulmonary metastases (Gadd et al 1993, Billingsley et al 1999). Median survival after detection of pulmonary metastases is <12 months (Van Glabbeke et al 1999).

Lymph node metastasis is rare, and occurs in 3-4% of STS. Certain histological subtypes, namely rhabdomyosarcoma, epitheloid sarcoma, clear cell sarcoma, angiosarcoma, and possibly synovial sarcoma, metastasize more readily to regional lymph nodes (Fong et al 1993, Riad et al 2004, Andreou et al 2009). Even incorporating sentinel node biopsy into the treatment of these extremely rare sarcomas has been considered (Andreou et al 2009).

Several well-established prognostic factors for oncological endpoints have been identified in large series, and are presented in Table 6.

TABLE 6. Negative prognostic factors for STS survival

Oncological endpoint	Negative prognostic factors	References
LRFS	Tumor size >10cm, high tumor grade, positive surgical margins, extracompartmental tumor location, recurrent tumor at presentation, age >50 (>64), MFH/neurogenic-/epitheloid sarcoma	Vraa et al1998, Stojadinovic et al 2002, Eilber et al 2003, Zagars et al 2003 (A)
MFS	Tumor size >5cm, high tumor grade, positive microscopic margin, leiomyo-/synovial-/neurogenic-/rhabdomyo-/epitheloid sarcoma, (tumor depth?)	Gustafson 1994 (B), Stojadinovic et al 2002, Pisters et al 1996 (B), Zagars et al 2003 (A)
DFS	Tumor size >5cm, high tumor grade, positive surgical margins, recurrent tumor at presentation, head/neck or deep trunk localization, age >64, rhabdomyo-/epitheloid-/clear cell sarcoma, (tumor depth?)	Zagars et al 2003 (A), Kotilingam et al 2006
DSOS	Tumor size >5cm, high tumor grade, positive surgical margins, extracompartmental tumor location, head/neck or deep trunk localization, age >64, rhabdomyo-/epitheloid-/clear cell sarcoma	Vraa et al 1998, Stojadinovic et al 2002, Zagars et al 2003 (A)

LRFS = Local recurrence-free survival, MFS = Metastasis-free survival, DFS = disease-free survival, DSOS = Disease-specific overall survival.

Among 504 STS patients treated at MDACC developing local or systemic recurrence during follow-up, 25% of recurrences were detected in the first 6 months, and 50% within 1 year and 2 months. 75% of all recurrences had

developed by 2 years and 3 months. At 5 years 93% of recurrences had developed, but 3% of all recurrences took longer than 10 years to develop (Zagars et al 2003 (C)).

In a U.S. report on 3479 patients from the National Cancer Database, including all anatomical sites and histological grades, the 5-year DSOS was 55.3%. DSOS by stage (AJCC 4th ed) was: stage I = 84.8%, II = 68.9%, III = 62.1%, IV = 19.2% (Pollock et al 1996). In 1225 patients with localized STS treated with surgery and radiotherapy in at MDACC in 1960-1999, Zagars et al reported the following 5-year survival figures: LRFS 83%, MFS 71%, and DSOS 73% (Zagars et al 2003 (A)). In a similar material from MSKCC on 1041 patients treated in 1982-1994, 5-year LRFS was 83%, MFS 68%, DFS 78%, and DSOS 76% (Pisters et al 1996 (B)).

In a more challenging subset of patients consisting of 459 high-grade, deep STS of the extremities and trunk treated by the Scandinavian Sarcoma Group in 1986-1993, 5-year LRFS was 77%, MFS 56%, and DFS 46% (Trovik et al 2001 (A)).

A series from the U.S. reported 5-year LFRS of 88% in 753 localized, intermediate- to high-grade extremity STS, with 90% LRFS for 607 primary tumors, and 81% for 146 patients presenting with recurrent tumors at presentation. Overall 5-year survival was 70%, with no significant difference between primary and recurrent tumor groups (Eilber et al 2003).

Lehnhardt et al reported on 140 patients with localized MFH, treated in Bochum, Germany in 1996-2004. LRFS was 74%, and OS 72% (Lehnhardt et al 2008), which is similar to results on 460 patients with localized MFH from MDACC, with LRFS of 78% and OS 73% (Zagars et al 2003 (A)).

In a small series of 62 mainly primary, subcutaneous extremity STS treated in Chicago in 1975-1993, LRFS was 95%, DFS 85%, and DSOS 87% (Gibbs et al 1997).

5.2 Surgical treatment of extremity soft tissue sarcoma

As local recurrence occurred in up to 90% of patients after simple excision (Weiss et al 2001), amputation became the treatment of choice for extremity STS (Cantin et al 1968, Hoekstra et al 2004). In the 1970's, however, introduction of the concept of surgical margins (Simon et al 1976) and the combination of surgery with RT helped to improve the results of limb-sparing treatment to match those of amputation (Rosenberg et al 1982). Today, limb-sparing multidisciplinary treatment is the standard treatment for extremity STS (Clark et al 2005).

5.2.1 Amputation vs. limb salvage

An amputation rate of 13% in localized extremity STS has been reported from MSKCC (Pisters et al 1996 (B)). Trovik et al found 15% amputations in 459 patients with localized, deep, high-grade lesions. Local recurrence rate was 4% in the amputation group compared to 26% after limb-sparing surgery. There was no difference in MFS, however (Trovik et al 2001 (A)). Eilber et al reported a 5% rate of amputation in 607 primary, localized, intermediate to high-grade extremity STS, and 13% for 146 patients with recurrent tumors (Eilber et al 2003). One study reported a 9.4% amputation rate in a high-volume sarcoma center compared to 13.8% in a low-volume center (Gutierrez et al 2007 (B)).

In a study on 408 sarcoma patients with lower extremity disease, 65 of which underwent amputation, limb salvage- and below-knee amputee-groups had similar oncological outcome. Amputation was, however, associated with decreased functional outcome and increased walking aid use, as well as with increased anxiety (Pardasaney et al 2006). A recent SSG study on 118 osteosarcoma patients showed significantly inferior functional outcome in amputees compared to patients treated with limb-sparing surgery, as measured by both Musculoskeletal Tumor Society (MSTS) score and Toronto Extremity Salvage Score (TESS). There was, however, no significant difference in quality of life (Aksnes et al 2008).

Even in the age of limb-sparing multi-modality treatment, amputation is sometimes the only feasible treatment option for extremity STS. Amputation should be considered when surgery, including advanced reconstructive techniques combined with RT and/or chemotherapy, cannot offer the patient a functionally acceptable, painless limb. Amputation should also be considered if the patient's general health or other diseases do not allow for the aforementioned therapies to be administered in a safe way. Finally, amputation should be offered as a palliative measure for patients with intractable pain, uncontrollable local symptoms (bleeding, skin ulceration, risk of infection), or a limb rendered useless by neurovascular infiltration (Clark et al 2003 (B), Pisters et al 2007(A)).

Amputation and prosthetic fitting is occasionally the fastest and most reliable way to achieve oncologic safety as well as acceptable functional results. This may be the case especially in lower leg, ankle and foot tumors, as modern below-knee prostheses permit a wide range of activities. In other anatomic sites, notably in the hand, the situation is quite different, and all effort is made to follow limb-sparing protocols (Colterjohn et al 1997, Zahlten-Hinguranage et al 2004, Ferguson 2005, Clark et al 2003 (B))

5.2.2 Reconstructive surgery

Extremity STS surgery frequently results in large soft tissue and bone defects, potentially leaving blood vessels, nerves, joints, or bones exposed. In addition, wounds need to heal well before postoperative oncologic treatment can be administered. For these reasons, and in order to achieve a good functional and aesthetic result, reconstructive procedures are frequently employed.

A "graft" is defined as tissue moved to a distant site without a vascular pedicle or vascular reconstruction. Conversely, a "flap" either retains its original blood supply via a pedicle (local and pedicled flaps), or has blood supply reestablished at the recipient site (microsurgical or free flap) (Yenidunya et al 2007).

Flaps can be classified according to the intended destination (local, pedicled or free flap) their blood supply (direct or indirect), their construction (uni-, bipedicled etc.), or their constituents. Flaps may consist of skin, fat, fascia (fasciocutaneous flaps), muscle (muscle flaps), or bone (osseous flaps) as well as nerve, intestine or omentum. Combinations of these, such as myocutaneous, osteocutaneous, osteofasciocutaneous, osteomusculocutaneous are frequently used (Hallock 2004, Hallock 2009 (B)).

Traditionally, reconstructive surgeons have used the "reconstructive ladder" (Table 7) in choosing the method of reconstruction, always attempting to use the simplest and safest method possible (i.e. lower down the "ladder"). Today, microvascular reconstruction is a safe procedure, and more sophisticated techniques, higher up the ladder, can be used to achieve superior results even when simpler methods are available (Mathes et al 1997).

TABLE 7. The "Reconstructive ladder"

Complexity	Reconstructive method
More complex	Free flap
	Pedicled flap
	Local flap
	Skin graft
Less complex	Direct closure

Modified from Willcox et al 2000

In 257 extremity STS patients treated at our institution, direct closure was possible in 41% of patients. Skin grafting only was used in 15%, local skin flaps in 5%, pedicled flaps in 12%, and microvascular flaps in 14% of patients (Popov 2005). Clarkson et al reported using pedicled flaps in approximately 20% and microvascular flaps in 5-10% of extremity STS patients (Clarkson et al 2004). In 42 patients with mostly trunk and lower extremity STS (including 14 DFSP), Papadopoulos et al reported direct closure in only 5%, whereas 83% of patients received pedicled and 12% free flaps (Papadopoulos et al 2006). A recent study found that sarcoma size >2.5 cm was associated with increased need for flap coverage in the hand (Talbot et al 2008).

Myocutaneous flaps provide well-vascularized tissue that withstands both RT and chemotherapy well, facilitating wound healing after tumor resection (Kane et al 1999, Spierer et al 2003, Temple et al 2007). There were less complications, fewer secondary procedures, greater limb salvage rate, and shorter hospitalization times among 41 patients that underwent flap reconstruction (36 free and 5 pedicled) as compared to a 37-patient direct closure group, when all patients had received preoperative RT (Barwick et al 1992). In a series of 173 extremity STS patients preoperatively treated with RT, major wound complications were as frequent in both direct closure and reconstructive surgery groups, although patients who were treated by the reconstructive surgery service were preoperatively considered high-risk patients for wound complications (Tseng et al 2006).

5.2.3 History of microsurgery

Pioneering work on vascular anastomoses was performed by Alexis Carrel who was awarded the Nobel Prize in 1912 for his work on vascular sutures and transplantation. He also experimented with extremity replantation in dogs as early as 1906 (Kocher 1995). The first to reportedly use an operating microscope was Swedish otolaryngologist Nylén. The binocular microscope was first used by Holmgren in 1923 (Armstrong et al 2001, Tamai 2009). In 1960 Jacobson and Suarez used the microscope to achieve successful anastomoses in small vessels of less than 1 mm diameter, pioneering microvascular surgical practice (Jacobson et al 1960).

In 1962 Malt performed the first successful macroreplantation of an extremity, reattaching the arm after traumatic above-elbow amputation (Malt et al 1964). The following year Kleinert and Kasdan managed the first successful microvascular revascularization of an ischemic thumb (Kleinert et al 1963). Komatsu and Tamai performed the first successful replantation of a completely amputated digit in 1965 (Komatsu et al 1968).

Cobbett reported the first toe-to-hand transfer in western literature in 1969 (Cobbett 1969), although toe-to-thumb transfers were done in China as early as 1966 (Buncke 1995, Tamai 2009). McLean and Buncke performed the first omental free flap in 1972 for a scalp defect (McLean et al 1972), and Harii performed the first cutaneous free flap in 1972 for hair transplantation (Harii et al 1974). Daniel and Taylor used the hypogastric flap for lower extremity reconstruction in 1973 (Daniel et al 1973). The 1970's saw the introduction of several new cutaneous and muscle or myocutaneous flaps, many of which are still among the most used free flaps. Ueba and Fujikawa pioneered free vascularized bone transfer in 1973 (Ueba et al 1983), although Taylor published the first reports in 1975-1976 (Taylor et al 1975, Taylor et al 1976). A more recent addition has been the introduction of perforator flaps by Koshima and Soeda in 1989 (Koshima 1989).

Transplantation of tissues between two individuals (allotransplantation) has its origin in the first organ transplant, a kidney transplant between identical twins performed by Murray in 1954 (Harrison et al 1956). Only three years later Peacock performed the first composite tissue allotransplant with an en bloc flexor tendon mechanism transplantation (Peacock 1960). More recent developments in the field of composite tissue allotransplantation were the first hand allotransplant in 1998 (Dubernard et al 1999), and the first facial allotransplant in 2005 (Devauchelle et al 2006).

5.2.4 Microsurgical reconstruction in extremity soft tissue sarcoma

The goals of reconstruction after STS surgery are wound coverage and tension-free closure, obliteration of dead space, restoration of form and of function when possible, as well as achieving a satisfactory aesthetic result. (Langstein et al 1999, Pederson 2001, Saint-Cyr et al 2006). The first report on using microvascular surgery to reconstruct defects after sarcoma surgery was from Japan in 1986, where two STS and four osteosarcoma patients were treated with free flap reconstruction (5 vascularized fibula and 1 gracilis muscle flap). One fibula flap was lost, but the authors concluded that the technique seemed

promising (Usui et al in 1986). Today, microvascular reconstruction is used for 12-18% of patients after resection of extremity STS (Lohman et al 2002, Kim et al 2004 (A), Popov et al 2005, Papadopoulos et al 2006). Free flap success rates after extremity STS surgery are 94-100%, equal to success rates in other indications (Barwick et al 1992, Hidalgo et al 1998, Johnson et al 2002, Kim et al 2004 (A), Basheer et al 2008).

5.2.4.1 Pedicled vs. free flaps

It has been stated that the only advantages of pedicled flaps over free flaps are shorter operative time, and lesser amount of expertise required (Kane et al 1999, Hoy 2006). Local and pedicled flaps disrupt local blood and lymphatic flow (Serletti et al 1998); some pedicled flaps also disrupt additional muscles in the affected limb, leading to further impairment of function. The use of adjacent and thus radiated tissue for coverage is discouraged in the setting of preoperative RT (Hoy et al 2006). Free flaps have been considered better suited particularly for large defects frequently cased by excisions of large, deep seated STS, in which RT and chemotherapy are required (Kane et al 1999).

Free flaps offer several advantages in extremity reconstruction after sarcoma resection (Figure 3). Large amounts of tissue with independent blood supply can be used without the limitations of rotational arcs. Composite flaps containing skin, fascia, muscle, bone, and even tendons, blood vessels, and nerves can be customized (Chang et al 2000, Carlson 2006). Flap safety is increased by using tissue from outside irradiated fields (Carlson 2006), and the well-vascularized tissue of free flaps is highly tolerant to wound complications, as well as to RT and chemotherapy (Peat et al 1994, Evans et al 1997, Kim et al 2004 (A), Ferguson 2005, Tseng et al 2006). High vascularity may even enhance delivery of chemotherapeutic agents to the resection site (Chang et al 2000). In a large series on 400 free flaps for oncological defects Disa et al reported 97% flap success rate, with all surviving flaps healing uneventfully, resulting in no delay in administration of RT or chemotherapy (Disa et al 1997).

FIGURE 3. Grade 3 subcutaneous MFH of the knee treated with a musculocutaneous ALT flap.

5.2.4.2 Choice of flap

A variety of flaps are available for each anatomic region, and to some extent, the method of reconstruction is dependent on the experience and preference of the surgeon. Some flaps have, however, been more frequently used than others in extremity reconstruction. Factors influencing free flap choice after tumor resection include recipient site-dependent factors such as defect location, size, and depth, types of tissue requiring reconstruction, need for functional reconstruction, and cosmetic considerations. In addition to these, flap reliability and also donor site-dependent factors such as the effect of previous surgery or RT, and donor site morbidity need to be considered.

Upper extremity

The shoulder region and upper arm can generally be reconstructed with a pedicled LD or thoracodorsal artery perforator (TAP) flap if previous treatment has not compromised the vascular pedicle. The LD can also be used in the arm as a (pedicled or free) functional flap when including motor innervation (Chang et al 2000).

For the elbow region, a pedicled radial forearm flap has been recommended. The functional free gracilis muscle is well suited for functional repair of finger and wrist flexion or extension (Langstein et al 1999, Chang et al 2000). Fascial or fasciocutaneous flaps such as the radial forearm, lateral arm, scapular, ALT or temporoparietal fascia flaps are thinner and may be superior to muscle flaps covered with skin grafts depending on the recipient site. Fascial flaps also make good gliding surfaces for tendons. (Willcox et al 2000, Pederson 2001, Saint-Cyr et al 2006).

When local solutions are not available for the forearm and hand, small free flaps such as gracilis, or serratus muscles are preferred (Langstein et al 1999, Chang et al 2000, Pederson 2001). Free toe transfer is a useful method for finger reconstruction (Pederson 2001).

Lower extremity

In the proximal lower limb pedicled rectus abdominis flaps can be used for reconstruction of a range of proximal thigh defects, whereas free flaps are required for reconstruction of large defects of the distal thigh. As large volumes are frequently needed, a free LD flap is useful (Langstein et al 1999).

Defects around the knee can generally be covered with pedicled gastrocnemius flaps, and pedicled soleus flaps can cover most middle lower leg defects (Langstein et al 1999, Chang et al 2000).

In the distal third of the leg local soft tissues are sparse and free flaps are frequently needed. For deep defects, reliable muscle or musculocutaneous flaps are preferred, although perforator flaps offer minimal donor morbidity and less bulk, achieving more precise restoration of form (Langstein et al 1999, Chang et al 2000).

For reasonably small defects of the distal lower leg, ankle and proximal foot, the fasciocutaneous sural flap can be used. (Levin 2008). Also thin ALT flaps can

be utilized, and in sole of foot reconstruction the ALT with the lateral femoral cutaneous nerve can be used as a sensorineural flap (Ferguson 2005). Flap sensibility in sole of foot reconstruction has, however, not been proven to prevent wound breakdown (Rautio 1991).

For long bone defects of the extremities the vascularized fibula flap, which can also be harvested as an osteocutaneous or osteomusculocutaneous flap, is preferred. A double-barrel configuration can be used in weight-bearing bones for additional stability (Pederson 2001, Saint-Cyr et al 2006).

After amputation, fillet flaps are useful for stump reconstruction and can cover defects of up to 50x70cm without any donor site morbidity (Langstein et al 1999, Chang et al 2000, Saint-Cyr et al 2006). In the case of finger amputation fillet flaps are useful for hand reconstruction and salvage (Talbot 2008).

5.2.4.3 Functional outcome after free flap reconstruction

Several authors have reported good functional outcome after extremity microvascular reconstruction. In a recent report from Japan on 19 sarcoma patients with microvascular reconstructions of the hand and forearm, mean MSTS score was 25.0 (Muramatsu et al 2009). Serletti et al found a mean MSTS score of 28.2 of 30 after free flap reconstruction in 16 patients with extremity sarcoma treated with limb salvage and RT. Lowest scores were for range of motion, whereas emotional acceptance scores were high (Serletti et al 1998). Contrary to these findings, Kim et al found low scores for emotional acceptance and also for manual dexterity in upper extremity microvascular reconstruction patients. In addition, lower average scores as compared to patients treated with non-microvascular reconstruction (MSTS score 20.1 vs. 24.1) were reported. The authors noted that the average scores seemed to improve with time, and more so in the microvascular group, the results being comparable between the two groups at 5 years (Kim et al 2004 (B)). A report on 54 patients treated with muscle flaps for extremity sarcomas found an average MSTS score of 27.1, but results of free flap and pedicled flap groups were not

compared (Hoy et al 2006). Similar results were reported in 55 sarcoma patients after flap reconstruction, with average MSTS score of 26.5 for upper and 21.4 for lower extremity patients (Morii et al 2009).

Rivas reported better function in 16 patients receiving free flaps than in 9 patients with pedicled flaps in the lower extremity after tumor resection (Rivas et al 2006), whereas Serletti found no difference in function between 17 pedicled and 16 free flap patients after extremity sarcoma resection (Serletti et al 1998).

Doi et al reported on 17 patients with extremity STS treated with free functional muscle flaps. Successful reinnervation was achieved in 16 flaps, and good functional results were achieved. The authors conclude by recommending functional reconstruction for young patients when tumor resection will result in severe loss of motor function (Doi et al 1999).

5.2.5 Forequarter amputation

Extremity amputation for curative treatment of malignant disease is performed when functionally acceptable results cannot be achieved with limb-sparing treatment. The other indication for amputation is palliation, i.e. relieving symptoms to improve quality of life even when there is no curative treatment option available.

Forequarter amputation includes the removal of the upper extremity with the scapula and part of the clavicle (Berger 1887). It is one of the most mutilating procedures in surgical oncology, but useful for curative and palliative treatment of proximal arm and shoulder girdle tumors (Keevil 1949, Malawer et al 2001). Several authors have modified the operative technique and approach, and the amputation can now be extended to include large chest wall resections when required (Littlewood 1922, Stafford et al 1958, Pressman 1974, Tukiainen et al 2003, Ferrario et al 2004).

Due to removal of the entire prominence of the shoulder, there is normally sufficient skin to close the wound primarily with a local fasciocutaneous flap as described in the original technique (Berger 1887). When larger skin defects are caused, reconstructive surgery is needed. Muscle transpositions have been used, but pedicles of local flaps are frequently located within fields of earlier surgery or RT and are thus of questionable reliability. For microvascular reconstruction, LD, RA and TFL flaps have been used (Cordeiro et al 2001). These can be combined with rib grafts, methylacrylate or mesh for chest wall stability (Arnold et al 1984). An alternative with the advantage of eliminating donor site morbidity is using a fillet flap from the amputated extremity (Figure 4), incorporating the underarm bones for chest wall reconstruction when required (Schmidt et al 1987, Kuhn et al 1994).

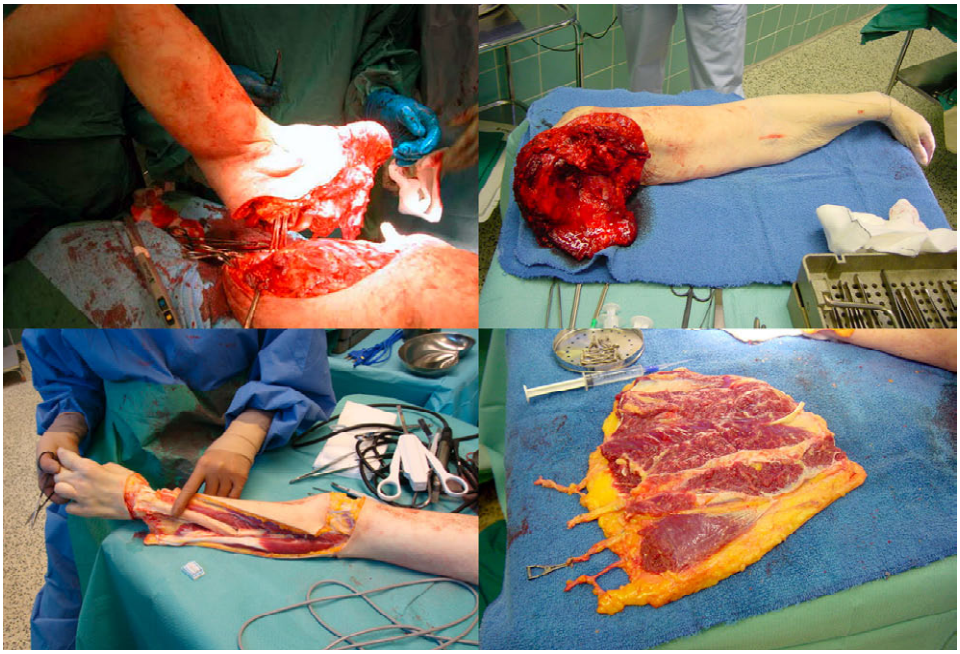

FIGURE 4. Preparation of the free forearm fillet flap after forequarter amputation.

5.2.6 Pulmonary metastasectomy

In 94 patients with a minimum follow-up of 5-years treated with pulmonary metastasectomy at the Roswell Park Cancer Institute in 1976-2000, actuarial 5-

year DFS was 5%, and OS 15% (Smith et al 2008). A recent review on pulmonary metastasectomy for STS reported 5-year overall survival rates of 25-38% for a select subgroup of patients with resectable metastases and a controlled primary tumor (Pfannschmidt et al 2009).

5.2.7 Prosthetic considerations

Functional results after tumor resection and limb sparing surgery are generally good to excellent (Serletti et al 1998, Kim et al 2004 (B), Rivas et al 2006, Wright et al 2008), also after free flap reconstruction (Morii et al 2009, Muramatsu 2009).

Modern lower limb and especially below-knee prostheses are very functional and permit several normal activities. Due to numerous ranges of motion required and the importance of manual dexterity, upper limb prosthesis functionality is poor as generally only one joint can be moved at a time (Kuiken et al 2007). Artificial limb use after forequarter amputation has been unpopular due to lacking functionality (Bhagia et al 1997, Clark et al 2003 (A)).

Technological advances in myoelectric prostheses, together with targeted reinnervation surgery and the development of new, improved neural machine interfaces have shown promising results. These allow intuitive control of multi-degree of freedom-prosthetic devices, and in one case even sensory feedback after targeted reinnervation surgery (Ohnishi et al 2007, Kuiken et al 2007, Kuiken et al 2009).

5.3 Oncologic treatment of extremity soft tissue sarcoma

The basis for modern treatment of extremity STS was laid with the realization that a combination of limb-sparing surgery and radiotherapy achieved local control rates equal to those seen after amputation (Rosenberger et al 1982). At present the routine use of adjuvant chemotherapy remains controversial and a subject of debate. Surgery remains the mainstay of, and the only curative

treatment for STS, but the majority of patients receive oncologic treatment, mainly radiotherapy, in addition.

5.3.1 Radiotherapy

Radiotherapy is combined with surgery to improve oncologic outcome, but has the potential to cause complications negatively affecting functional outcome. RT can be delivered either as external beam radiotherapy (EBRT), or less frequently as brachytherapy, which involves placing catheters containing radioactive material into the wound during surgery. Also the combination of both has been used (Alektiar et al 2005, Clark et al 2005).

Adjuvant RT improves local control rates in extremity STS, and the effect is more marked in deep-seated, high grade lesions (Yang et al 1998, Jebsen 2008). In 164 patients receiving postoperative brachytherapy, improved local control was seen only in high grade tumors (Pisters et al 1996 (A)). In prospective, randomized trials no improvement in disease-free or overall survival attributable to RT has been seen. Not all patients require adjuvant RT, however. A recent prospective study concluded that carefully selected patients with <5cm tumors could be safely treated with R0 resection only, requiring no further treatment (Pisters et al 2007 (B)), supporting earlier findings from retrospective studies (Rydholm 1991, Khanfir et al 2003).

Adjuvant EBRT can be given either pre- or postoperatively, and the sequencing of surgery and radiotherapy has been an issue of much debate. No difference in local control or survival has been shown between the two options, but smaller doses of radiation and smaller fields can be used when RT is given preoperatively (50 Gy) compared to postoperative administration (60-66 Gy) (Nielsen et al 1991, Clark et al 2005). This has been expected to increase radiation-related complications in postoperatively treated patients, as doses > 60 Gy have been shown to increase fibrosis and impair functional outcome (Robinson et al 1991). On the other hand, preoperative treatment may interfere with final histopathological examination (Suit et al 1985).

Retrospective reviews showed that preoperatively treated patients had more acute wound complications (Cheng et al 1996), but that postoperative treatment resulted in more late radiation-associated complications (Zagars et al 2003 (B)). In 2002, the results of a randomized, controlled, multi-center trial from Canada were published. This study and its follow-up showed 35% major wound complications after preoperative RT compared to 17% in the postoperatively treated patients. Wound complications were significantly more frequent in the lower extremity. No definitive difference in functional outcome was found, but the postoperatively treated patients had significantly more late fibrosis, and also more joint stiffness and edema, although the last two were not statistically significant findings. The authors conclude that the risk of immediate wound complications must be assessed for each patient depending on tumor location and weighed against the increased risk of late radiotherapy-associated complications and decreased functional outcome (O'Sullivan et al 2002, Davis et al 2005). Modern techniques of RT delivery with tighter dose control help reduce radiation-associated morbidity to the surrounding tissues, without compromising local control (Alektiar et al 2008).

Radiotherapy can also be used in the palliative setting for painful bone metastases or for tumors causing bleeding, compression symptoms or skin ulceration when operative treatment is not possible. Palliative radiotherapy is effective for decreasing spinal or mediastinal compression caused by metastatic disease (Kwok et al 2008)

5.3.2 Chemotherapy

It is generally agreed that resectable low-grade and small high-grade STS (AJCC Stage I-II) do not need routine chemotherapy (Pisters et al 2007 (B)). An effective chemotherapy regimen is, however, desperately needed to improve the outcome of patients with high risk tumors (AJCC Stage III), as survival rates in this group are poor. The favorable effect of chemotherapy on survival is confirmed in Ewing sarcoma, osteosarcoma, and rhabdomyosarcoma. The

majority of pediatric sarcoma patients undergo chemotherapy (Robinson et al 2008, Tunn et al 2009).

Adjuvant chemotherapy for STS is controversial. It has generally been based on doxorubicin alone or more recently in combination with ifosfamide, or in combination with mesna, ifosfamide and dacarbazine (MAID protocol). A meta-analysis by the Sarcoma Meta-Analysis Collaboration from 1997, including 14 randomized controlled trials, found improved rates of LRFS, MFS, and DFS, but no statistically significant improvement in OS in patients with localized, resectable STS (Sarcoma Meta-Analysis Collaboration 1997). In an updated meta-analysis, including the previous 14 and 4 new studies, a small but statistically significant improvement in all endpoints could be seen. A 3-5% absolute risk reduction was seen for local recurrence, 9-10% for distant recurrence and 9-12% for overall recurrence in patients receiving adjuvant chemotherapy. An absolute risk reduction of 6% (95% CI 2-11%, $p = 0.003$), from 46% to 40% risk of death was shown in all studies combined. In addition, in five studies where doxorubicin was combined with ifosfamide, the absolute risk reduction was 11% (95% CI 3-19%, $p = 0.01$), with risk of death reduced from 41 to 30%. The authors conclude, however, that the statistically significant findings are not necessarily clinically significant, and that use of adjuvant chemotherapy should be based on individual evaluation of each patient and the risks of chemotherapy (Pervaiz et al 2008). As noted by Pisters et al, it should be kept in mind that while the survival benefit of chemotherapy may be controversial in studies containing all STS subtypes, the effect may be more marked in chemosensitive histological types such as synovial and round cell sarcoma (Pisters et al 2007 (A)). Given the rarity of STS, and the even greater rarity of individual subtypes, it will be very difficult to produce reliable evidence of such an effect.

In addition to the possible benefits of chemotherapy on survival, chemotherapy has been used preoperatively for downstaging tumors prior to surgery (Pisters 2007(C)). One study found that downstaging led to a decrease in the planned extent of surgery in 13% of patients. Regrettably, tumor progression during

preoperative RT treatment led to an increase in the extent of surgery in 9% of patients (Meric et al 2002).

A recent randomized study showed improved rates of local recurrence-free and disease-free survival after treatment with neo-adjuvant chemotherapy and local hyperthermia compared to chemotherapy alone (Issels et al 2010)

Chemotherapeutic treatment of metastatic STS is palliative in nature (Clark et al 2005). The most commonly used chemotherapeutic agents are doxorubicin and ifosfamide, followed by taxanes and gemcitabine (Pisters et al 2007(A), Maki 2007, Grimer et al 2010). A new drug of some interest in the palliative chemotherapy setting is trabectidin. It has, however, proven to be moderately to highly toxic, with mainly hematologic and hepatic adverse effects (Clark et al 2005, Boudou et al 2009, Le Cesne et al 2009). Seemingly better tolerated is the receptor tyrosine kinase inhibitor panzopanib, which in a phase II study in 142 patients showed freedom from progression at 12 weeks in 39-44% of patients with non-adipocytic STS (Sleijfer et al 2009).

5.3.3 Isolated limb perfusion

Principally used in Europe, isolated limb perfusion (ILP) is an approach for the treatment of locally advanced, limb-threatening extremity STS. By isolating it from central circulation, the extremity can be perfused with concentrations of chemotherapeutic agents that would otherwise be lethal to the patient. Initial trials with melphalan had little effect, but when combining melphalan with tumor necrosis factor (TNF) alpha and mild local hyperthermia, ILP achieved high rates of tumor response, and limb-sparing surgery is possible in 70-100% of patients. However, there seems to be no benefit in overall survival rates, and up to 10 % of patients suffer from severe locoregional toxic effects (Mocellin et al 2006, Hohenberger et al 2008, Tunn et al 2009)

5.3.4 Molecularly targeted approaches

New molecularly targeted treatment strategies have had a major impact on the treatment of gastrointestinal stromal tumor (GIST) with imatinib and similar drugs (Blanke et al 2008). Imatinib has also shown effect in the treatment of DFSP (McArthur 2007), but while other molecularly targeted therapies are currently being investigated in the treatment of STS, so far no clinical breakthroughs have been reported (Mocellin et al 2006).

5.4 Multidisciplinary group approach

Due to the rarity of STS very few physicians are familiar with these tumors and their treatment. The cooperation of surgeons, oncologists, pathologists and radiologists is required for optimal treatment. This has prompted the formation of specialized multidisciplinary groups (Rydholm 1997).

The beneficent effect of multidisciplinary care was demonstrated first in Scandinavia. Gustafson et al showed that the risk of local recurrence was increased 2.4-fold if patients were not referred to specialist centers, and 1.3-fold if referred only after primary surgery elsewhere (Gustafson et al 1994 (A)). Results of treatment at HUCH improved drastically after the 1987 formation of a soft tissue sarcoma group: 3-year DFS among patients treated in 1960-1975 was only 36%, whereas the corresponding figure was 69% in patients treated by the multidisciplinary group in 1987-1993 (Wiklund et al 1996). In 1851 patients treated in Sweden and Norway in 1986-1997, local recurrence rate was 70% in patients treated outside sarcoma centers, and only 20% in patients primarily treated at sarcoma centers (Bauer et al 2001).

Mankin et al demonstrated that biopsy-related errors and complications such as major errors in histological diagnosis, technically poor biopsies, wound complications, change in outcome and even unnecessary amputations, were 3-5 times more likely when the biopsy was performed at the referring institution compared to the sarcoma center (Mankin et al 1982). In a follow-up study,

results were much the same; errors and complications were 2-12 times more likely after biopsies performed at the referral center (Mankin et al 1996).

Clasby et al demonstrated serious shortcomings in the treatment of STS in Britain, including lacking histology reports, insufficient surgical margins, ignoring necessary further treatment in 67%, and lack of follow-up in 12% of patients. The authors concluded that these rare tumors should be treated in specialist centers (Clasby et al 1997).

A small series from France showed that only 57% of STS patients had pre-treatment sarcoma group evaluation, and only 42% had biopsy prior to surgery. A 6% rate of local recurrence in patients operated by a dedicated sarcoma surgeon, compared to 44% in patients operated by other surgeons was also reported (Ray-Coquard et al 2004). When reviewing 104 cases of STS that were initially managed outside specialist institution and later referred to Huntsman Cancer Institute, the authors found that 37% of histological diagnoses changed on review. In addition, 82% of margins deemed wide or excisional at the referring institution were in fact margin positive (Randall et al 2004).

Bhangu et al compared the results of 96 patients treated at a specialist centre with those of 164 patients treated in 38 district general hospitals in the UK in 1994-1996 with a minimum follow-up of 5 years. Local recurrence rate was 39% for patients treated at a district general hospital, compared to 19% in the specialist centre. 5-year OS was 58% in both groups, although the specialist centre treated significantly more patients with large, deep, high-grade tumors (Bhangu et al 2004).

6. AIMS OF THE STUDY

I To evaluate the suitability of free flap reconstruction after soft tissue sarcoma resection near the knee and the feasibility of immediate collateral ligament reconstruction.

II To assess the safety and reliability of free flap use after soft tissue sarcoma surgery in the lower extremity, and to evaluate the impact on functional outcome.

III To study the results of microvascular reconstruction of bone and soft tissue defects after soft tissue sarcoma resections in the upper extremity and implications on upper extremity function.

IV To examine the results of forequarter amputation for malignancy and the microvascular reconstructive procedures used.

7. MATERIALS AND METHODS

HUCH soft tissue sarcoma group protocol

The HUCH soft tissue sarcoma group was founded in 1987 and consists of oncologists, plastic surgeons, pathologists and radiologists. In weekly meetings, each individual patient is evaluated, and treatment is planned.

Referral status was defined as virgin primary if no procedures or needle biopsy only had been performed. Patients were considered to have been referred after intralesional operation when either open biopsy or intralesional operation had been performed. When a sarcoma had been previously considered widely excised and later recurred, referral status was defined as recurrent tumor.

Core- or fine-needle biopsy was used to specify histology and grade. Needle biopsies were mainly performed under ultrasonography guidance, CT guidance being used in select cases. Clinical examination as well as MRI and CT imaging were used for evaluating local and systemic status. For tumor grading, a four-stage scale was used, with grades 1-2 representing low-grade tumors, and grades 3-4 representing high-grade tumors. Tumor size was defined as largest diameter of the tumor before sample fixation, as measured by the pathologist.

A tumor was considered to be subcutaneous if situated entirely in the subcutaneous space without infiltrating the underlying muscle fascia. A tumor completely located within a muscle was considered to be intramuscular. Both subcutaneous and intramuscular tumors, as well as ones situated inside a muscle compartment without compromising the intercompartmental fascia were defined as intracompartmental. Any tumor infiltrating a fascial plane between the subcutaneous tissue and an underlying muscle, or penetrating an intercompartmental fascia was defined as extracompartmental. All bone-infiltrating tumors were also considered extracompartmental.

Surgical margins were defined as wide if the tumor was surrounded by no less than 2.5 cm of healthy tissue in microscopical examination, or if an intact fascia separated it from the resection margin. Excision was also considered to be wide after myectomy of a muscle containing an intramuscular tumor. If the microscopic tumor-free margin was less than 2.5 cm, but no tumor cells were found at the edge of the specimen, resection was considered marginal. If, however, malignant cells were present at the edge of the specimen, margins were considered intralesional.

When wide surgical margins were achieved, no further treatment was considered necessary. Marginal surgery was followed by postoperative RT at a dose of 50 Gy during 5-6 weeks, with an optional 10 Gy boost. Intralesional margins were not accepted, and re-operation aimed at wider margins. If necessary, amputation was performed.

Treatment was considered adequate after wide resection, or after marginal surgery combined with postoperative RT. Marginal surgery alone, or intralesional margins not leading to re-operation were considered inadequate.

Selected patients with large tumors received preoperative RT to improve resectability. In the early years of the sarcoma group, neoadjuvant or adjuvant chemotherapy was administered only to patients with extraskeletal Ewing's sarcoma and related tumors. Later, adjuvant chemotherapy indications were modified to include age less than 70 years, high tumor grade, and two of the three following factors: tumor size > 8.0 cm (5.0 cm for synovial sarcoma), tumor necrosis, or vascular invasion in histopathological examination

Follow-up length for STS was five years if no disease recurrence occurred. High-grade lesions were followed at two-month intervals during the first year, and every six months after that. For patients with low-grade tumors, follow-up interval was 4-6 months throughout follow-up. In addition to clinical examination, ordinary chest X-ray was performed during each visit. CT or MRI of the operative area was performed annually, beginning at six months after operation.

Patients and methods (Studies I-IV)

The study population consisted of a total of 116 patients that underwent 118 operations at Helsinki University Central Hospital (HUCH) or Oulu University Hospital (OUH). There were 95 patients treated for STS with curative intent, and these were included in final survival analysis. Median age was 55 years (range 13-85), with 58 males (50%), and 58 females (50%). Tumor characteristics are given in Table 8.

Patient records of HUCH and OUH were retrospectively reviewed for data on patient demographics, treatment details and outcome. When necessary, data on long term-follow up and functional result was acquired from other hospitals.

Patients and methods (Study I)

15 patients treated by the HUCH soft tissue sarcoma group in 1993 – 2005 for STS at near the knee joint requiring free flap reconstruction after tumor excision were included. There were 6 male and 9 female patients. Median patient age was 66 years. Eight patients were referred for virgin primary tumors, 2 for primary tumors after intralesional operation, and 4 for recurrent tumors.

Patients and methods (Study II)

73 lower extremity tumor patients were treated with free flap reconstruction were included. 15 patients had a resection of STS in the knee area, and had been previously included in study I. 72 patients were treated for STS, and one for recurrent malignant villonodulary synovitis. All patients were treated with curative intent. There were 31 male and 42 female patients, and median age was 53 years. 32 patients were referred for virgin primary tumors, 22 for primary tumors after intralesional operation, 14 for recurrent tumors and 5 for complications after recent STS surgery.

TABLE 8. Tumor characteristics of 116 patients

	Study				%
	II* (n=73)	III (n=20)	IV** (n=23)	Total (n=116)	
Tumor size (cm)					
Median	6.0	5.0	10.0	6.0	
Range	1.2 - 35.0	1.8 - 29.0	5.2 - 29.0	1.2 - 35.0	
Tumor location					
Foot	10			10	8.6
Ankle	3			3	2.6
Lower leg	20			20	17.2
Knee	18			18	15.5
Thigh	9			9	7.8
Hip region	13			13	11.2
Hand		1		1	0.9
Wrist		2		2	1.7
Forearm		13		13	11.2
Elbow		1		1	0.9
Upper arm		2	1	3	2.6
Shoulder		1	22	23	19.8
Histopathologic diagnosis					
MFH	37	8	8	53	45.7
Synovial sarcoma	9	2	1	12	10.3
Leiomyosarcoma	7			7	6.0
Fibrosarcoma	2	2	2	6	5.2
Sarcoma NOS	3	2	1	6	5.2
MPNST	1	1	2	4	3.4
Myxoid liposarcoma	4			4	3.4
Ductal carcinoma (of breast)			3	3	2.6
Angiosarcoma			2	2	1.7
Chondroblastic osteosarcoma			2	2	1.7
Epitheloid sarcoma	1	1		2	1.7
Adenocystic carcinoma			1	1	0.9
Borderline mesenchymal tumor	1			1	0.9
Chondrosarcoma	1			1	0.9
Dedifferentiated chondrosarcoma	1			1	0.9
Desmoid tumor		1		1	0.9
DFSP		1		1	0.9
Extraskeletal chondrosarcoma		1		1	0.9
Extraskeletal osteosarcoma	1			1	0.9
Liposarcoma	1			1	0.9
Malignant hemangiopericytoma	1			1	0.9
Malignant villonodulary synovitis	1			1	0.9
Myxoid MFH		1		1	0.9
Myxofibrosarcoma	1			1	0.9
Pleomorphic liposarcoma	1			1	0.9
Spinocellular carcinoma			1	1	0.9
Tumor malignancy grade* **					
High	56	16	18	90	77.6
Low	16	2		18	15.5
Tumor compartment					
Extracompartmental	45	17	23	85	73.3
Subcutaneous	24	3		27	23.3
Other intracompartmental	4			4	3.4
SUM	**73**	**20**	**23**	**116**	

* All 15 patients in Study I are included in Study II. ** Two patients included in both Study III and IV are reported only with Study III. *** Grade is given for soft tissue sarcomas only. MFH = Malignant fibrous histiocytoma, NOS = Not otherwise specified, MPNST = Malignant peripheral nerve sheath tumor, DFSP = Dermatofibrosarcoma protuberans.

Patients and methods (Study III)

20 patients with upper extremity tumors treated by the HUCH soft tissue sarcoma group in 1990 – 2006 with free flap reconstruction were identified. 18 patients were treated for STS and one each with desmoid tumor and dermatofibrosarcoma protuberans (DFSP). Of the 18 STS patients, 16 were treated with curative intent. There were 16 male and 4 female patients with a median age of 61 years. 7 patients were referred for virgin primary tumors and 6 for primary tumors after intralesional operation. 7 patients were referred for recurrent tumors.

Patients and methods (Study IV)

25 patients treated with FQA in 1989-2008, 20 at HUCH and 5 at OUH, were included. Two of these patients had been previously included in Study III. For each individual patient, the most suitable method of FQA was utilized, the most common being a combined anterior-posterior technique. Microscopical tumor-free margins were determined only for curatively treated patients, and only if the surgeon considered the resection macroscopically wide.

All patients were operated on under general anesthesia with additional epidural or brachial plexus anesthesia used frequently later in the series.

Surgical treatment

Patients were treated according to the HUCH soft tissue sarcoma group protocol where applicable. Limb-sparing excision of a lower extremity tumor was performed in 73 patients, and of an upper extremity tumor in 18 patients.

In all studies combined, 105 free flap operations were performed on 103 patients. The free latissimus dorsi was the most frequent free flap, used in 59 cases (56%). Details of free flap procedures are presented in Table 9.

TABLE 9. Data on 105 free flap procedures

	Study			
	II* (n=75)	**III** (n=20)	**IV**** (n=10)	**Total** (n=105)
Operative time (min)				
Mean	355	310	355	350
Range	180 - 805	195 - 575	305 - 570	180 - 805
Flap ischemia time (min)				
Median	70	64	79	69
Range	26 - 268	31 - 216	26 - 162	26 - 268
Operative blood loss (ml)				
Median	1325	650	4125	1300
Range	200 - 6300	150 - 8000	2600 - 9400	150 - 9400

Free flap					**%**
Latissimus dorsi	54	5		59	56.2
Anterolateral thigh	9	1		10	9.5
Tensor fascia latae	3	3	4	10	9.5
Forearm fillet		2	6	8	7.6
Radial forearm	4	4		8	7.6
Fibula	1	2		3	2.9
Gracilis	3			3	2.9
Scapularis		2		2	1.9
Rectus abdominis	1			1	1.0
Replantation of forearm		1		1	1.0
SUM	**75**	**20**	**10**	**105**	

* All 15 patients in study I are included in study II. ** Two patients included in both Study III and IV are reported only with Study III.

In study I, when radical resection of a tumor near the knee joint required excision of the collateral ligaments these were sacrificed. When knee instability resulted, reconstruction of the collateral ligaments was performed using bone-patellar tendon-bone graft in six patients (three medial and three lateral ligaments), and pes anserinus tendon transposition in one patient (medial ligament). External femorotibial fixation was used for 4-6 weeks postoperatively before mobilization was allowed.

In study II, wide surgery was attempted when possible. All defects were reconstructed with free flaps, and two patients needed two free flaps for reconstruction.

In study III wide excision of extremity tumors was attempted in 18 out of 20 patients. Two patients were treated with primary forequarter amputation. All defects were reconstructed using microvascular flaps.

In study IV, wound closure after FQA was achieved by using local fasciocutaneous flaps when permitted by the width of resection. Extended FQA with chest wall resection was performed in seven patients, and reconstruction of chest wall stability using free forearm fillet flaps, or with free rib grafts and synthetic mesh was necessary for three of these patients. When free flap reconstruction was deemed necessary, a fillet flap from the amputated extremity was preferred. When the fillet flap was not available, coverage was achieved with the ipsilateral TFL (Figure 5). When resection resulted in instability of the chest wall, reconstruction including fillet flap bones, rib grafts, or synthetic mesh was performed.

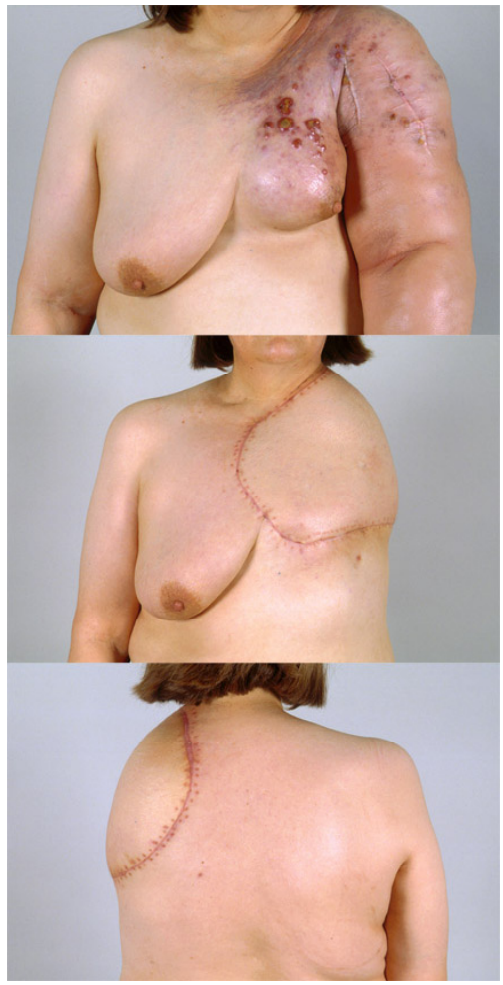

FIGURE 5. Pre- and postoperative view of patient treated for recurrent ductal carcinoma of the breast with forequarter amputation and reconstruction using a microvascular TFL flap.

Statistical analysis

For statistical analysis, SPSS for Windows (v 13.0, SPSS Inc., Chicago, IL) was used in studies I-II, and SPSS for Windows (v 15.0, SPSS Inc., Chicago, IL) in studies III-IV. Estimated 5-year survival figures were calculated according to the

Kaplan-Meier method. Survival differences between groups were analyzed using Log-rank test in a univariate model, and significant factors were further analyzed in a multivariate model using Cox regression analysis. Factors affecting surgical complications were analyzed by chi-square- or Fisher's exact tests. Statistical significance was set at 0.05.

8. RESULTS

Complications

One patient died during the first postoperative month from a pulmonary infection, after curatively intended excision of a 7cm high-grade MFH of the knee. Four flaps were lost, giving a free flap success rate of 96%. All flaps lost were for reconstruction of lower extremity defects (Study II).

Microvascular anastomosis complications necessitating reanastomosis but not resulting in flap loss occurred in 9 of 105 free flap procedures (9%). Anastomosis complications occurred in 1 patient (7%) in Study I, 6 patients (8%) in Study II, 2 patients (10%) in study III, and 2 patients (17%) in study IV.

Wound complications requiring operative room revision occurred in 18 of 116 patients (15%). Wound complication rates for studies I-IV were 27%, 26%, 15%, and 8%, respectively.

One patient developed severe respiratory failure after extended forequarter amputation with resection of ribs I-III, the clavicle, and part of the sternum. This was managed with temporary mechanical ventilatory support, and the patient recovered without further surgery.

Of the studied factors (patient age, smoking status, diabetes, ASA-group), none achieved statistical significance in predicting surgical complications in the separate studies. When combining all 116 patients, the only significant predictor for wound complications was patient age >55 years. 12% of 60 patients of 55 or younger underwent wound revision, compared to 28% of 58 patients over 55 (p=0.037). A non-significant correlation was seen between smoking and wound complication; 17% of non-smokers underwent surgery for wound complications, whereas the corresponding number for smokers was 25%.

Surgical margins and oncologic treatment

In 95 STS patients treated with curative intent, surgical margins were wide in 43 patients (45%), marginal in 47 (49%), and intralesional in 5 (5%). Achieved margins were comparable in the upper and lower limb. Postoperative RT was delivered to 38 of 47 patients (81%) with marginal excision. In 6 patients (13%) postoperative RT could not be administered because of previous treatment. Three patients (6%) received no RT despite marginal excision. Of five patients with intralesional excision, two underwent immediate amputation, and three had no further surgery (due to disease spread or patient refusal).

Of 95 curatively treated STS patients, 7 were administered preoperative RT, and 57 were administered postoperative RT. Neoadjuvant chemotherapy was used in 5 cases, and 14 patients received adjuvant chemotherapy.

Adherence to sarcoma group protocol

Out of 95 curatively treated patients with extremity STS, 89 (94%) were treated according to sarcoma group protocol. In three patients with marginal surgical margins, RT was omitted after sarcoma group deliberation, based on tumor characteristics. In three patients with intralesional margins that did not undergo further surgery or amputation, two refused recommended amputation and one developed rapidly progressing disease with multiple metastases by the time the surgical margin was determined.

Knee stability after sarcoma resection in the knee (Study I)

Collateral ligament excision was done in 9 of 15 patients in Study I. Two lateral ligaments were not reconstructed, resulting in lateral knee instability and subsequent need for orthosis in one patient. Four medial and three lateral ligaments were reconstructed. One patient with medial collateral ligament reconstruction suffered recurrent dislocations of the patella, and later underwent

correctional surgery. None of six patients undergoing tumor excision without collateral ligament resection suffered from knee instability.

Functional outcome after limb-salvage surgery (Studies II and III)

After tumor excision and free flap reconstruction in the lower extremity (Study II), 64% of patients could walk normally, 11% had a mild walking impairment not necessitating ambulatory aids such as crutches, walking aids or prostheses. 21% required aids in order to ambulate, and 4% needed a wheelchair.

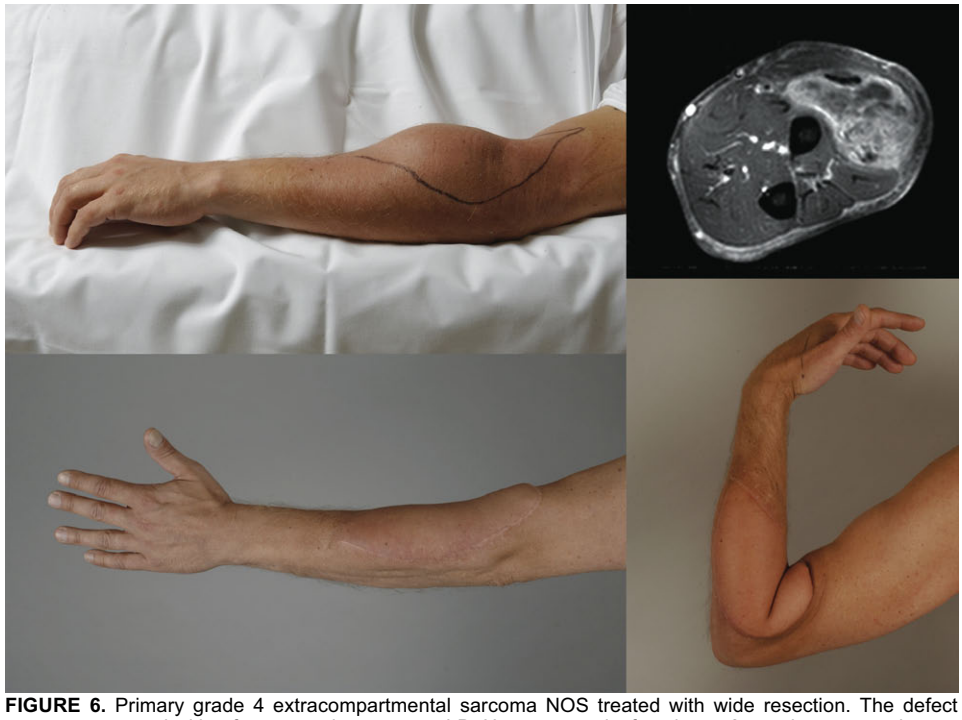

FIGURE 6. Primary grade 4 extracompartmental sarcoma NOS treated with wide resection. The defect was reconstructed with a free musculocutaneous LD. Upper extremity function at 8 months was good.

In 18 upper extremity patients undergoing limb-sparing resection and free flap reconstruction (Study III), upper limb function was unaffected in 44% (Figure 6), and mildly impaired but not influencing daily life in 11% of patients. 39% of patients regained an accessory upper extremity only. One patient underwent transhumeral amputation because only intralesional surgical margins were achieved despite attempted limb-salvage.

Management of postoperative pain in forequarter amputees (Study IV)

Of 25 forequarter amputees, 11 (44%) developed phantom limb pain after amputation. The pain was controlled by pharmacological means or decreased with time, and only three patients (12%) experienced significant phantom pain at 6 months. Two patients died of their disease while still suffering from phantom pain, at 2 and 8 months after operation respectively.

Thirteen patients (52%) underwent amputation under general anesthesia, 7 (28%) also received epidural anesthesia, and 5 (20%) were administered additional brachial plexus anesthesia. There was no statistically significant correlation between perioperative pain management and development of postoperative or long-term phantom limb pain.

Patients using opioids for pre-amputation pain were more likely to develop phantom limb pain (70 vs. 27%, $p = 0.049$).

Oncologic outcome and prognostic factors

Patients treated with palliative intent, and patients with tumors other than soft tissue sarcomas were excluded from survival analysis. For the remaining 95 patients, median follow-up was 61 months (range 0-218). Estimated 5-year survival figures for the entire population and the separate studies are presented in Table 10.

In Study II, no statistically significant factors predicting local recurrence were identified. Adverse prognostic factors for metastasis, disease recurrence, and disease-specific overall survival in multivariate analysis were tumor size >5.0cm, and extracompartmental location of tumor. In Study III, tumor size predicted both local recurrence and death of disease in univariate analysis. Tumor grade was an adverse prognostic factor for local recurrence only in univariate analysis. In Study IV, palliatively intended treatment was a significant adverse prognostic factor for disease specific death.

When combining all the 95 curatively treated STS patients, significant prognostic factors for LRFS, MFS and DFS were extracompartmental tumor location and tumor size >5cm. For DSOS, only extracompartmetal location of tumor was significant. High tumor grade was significant in univariate analysis for LRFS, DFS and DSOS, but lost significance in multivariate analysis.

TABLE 10. Outcome of curatively treated soft tissue sarcoma patients

	Study				**Total**
	I* (n=15)	**II** (n=72)	**III**** (n=16)	**IV** (n=8)	(n=95)
Follow-up (months)					
Median	71	60	74	25	61
Range	0 - 121	2 - 224	19 - 176	5 - 218	0-224
LRFS (%)	91.7	81.7	56.5	33.3	73.1
MFS (%)	59.5	58.8	66.4	37.5	58.3
DFS (%)	59.5	55.5	45.0	12.5	50.1
DSOS (%)	76.2	70.4	80.2	31.2	68.9

* All 15 patients in study are included in study II. ** One patient included in study III is also included in study IV. LRFS = Local recurrence-free survival, MFS = Metastasis-free survival, DFS = disease-free survival, DSOS = Disease-specific overall survival.

9. DISCUSSION

Oncological outcome

The treatment of extremity STS has changed fundamentally in the last 40 years as primary amputation has been replaced by limb-sparing multimodality treatment. Through centralization of care it has become possible for individual physicians to evaluate and treat significant numbers of these rare tumors.

Oncological outcome is the foremost concern in the treatment of the surgical cancer patient. In the present studies 94% of patients received treatment as recommended by the HUCH soft-tissue sarcoma group. 5-year LRFS was 81.7% in lower extremity STS, but only 56.5% in upper extremity disease. 5-year DSOS was excellent in both groups, however, 70.4% in the lower and 80.2% in the upper extremity (Table 10). These are comparable to other studies, although direct comparison is difficult due to heterogeneous study populations (Table 11).

TABLE 11. Oncological outcome in studies on soft tissue sarcoma

Author	n	Extremity	Percent >5cm	Percent high grade	Percent deep	Percent recurrent	5-year LRFS	5-year MFS	5-year DFS	5-year DSOS
Pisters et al 1996 (B)	1041	upper/lower	na	60	na	na	83	78	68	76
Gibbs et al 1997	62	upper/lower	32	74	0	0	95	na	81	87
Vraa et al 1998	316	extr + trunk	50	65	59	18	79	na	na	74
Popov et al 2000	106	lower	41	77	68	19	79	72	63	76
Trovik et al 2001 (A)	459	extr + trunk	45 (>9cm)	100	50	20	77	56	46	na
Lohman et al 2002	100	upper	47	70	56	25	87	na	na	82
Eilber et al 2003	146	upper/lower	74	53	na	0	90	na	na	70
Eilber et al 2003	607	upper/lower	74	72	na	100	81	na	na	70
Zagars et al 2003 (A)	1225	extr + trunk	59	71	na	16	83	71	na	73
Kim et al 2004 (A)*	17	upper	47	94	na	71	50	na	na	61
Popov et al 2004	80	upper	52	84	69	19	79	68	62	75
Lehnhardt et al 2008	140	upper/lower	78	66	79	66	74	na	na	72

* 16 patients treated with microvascular reconstruction. LRFS = Local recurrence-free survival, MFS = Metastasis-free survival, DFS = disease-free survival, DSOS = Disease-specific overall survival, na = data not available.

Most upper extremity sarcomas in study III were located distal to the elbow, the more proximal ones requiring microvascular reconstruction less frequently, as

pedicled flaps can be readily used. The seemingly high rate of local recurrences in study III (LRFS 56.5%, Table 10) may reflect the challenging anatomical setting; a high density of vital structures may make achieving sufficient surgical margins in the forearm and hand difficult. Also, the patient material included 86% high-grade, and 86% extracompartmental tumors (compared to 78 and 61% in study II, respectively). Further, the survival analysis of upper extremity STS included only 16 curatively treated STS patients, decreasing statistical power. Interestingly, the only other study published on upper extremity microvascular reconstruction after STS surgery reports very similar outcome (LRFS 51%), although 71% of tumors in that series were recurrent (compared to only 25% in study III) (Kim et al 2004 (A)).

Suitability of free flap reconstruction in soft tissue sarcoma surgery

Free flap success rate in this series was 96%, a rate comparable to other studies on free flap use for reconstruction after oncologic surgery (Barwick et al 1992, Disa et al 1997, Hidalgo et al 1998, Kim et al 2004 (A)). Microvascular reconstruction is thus a safe procedure for STS patients, with low complication rates. In order to identify patients at greater risk for flap loss or anastomosis complications, larger studies need to be undertaken; in this series no factors associated with flap-related complications were identified.

It is conceivable that the importance of free flap reconstruction after oncologic surgery may increase in the future as the improvement in survival rates has allowed for a shift of focus towards preservation or restoration of function (and even of cosmesis when possible). At the same time, as reliability of free flaps has increased, reliance on the reconstructive ladder has decreased (Willcox et al 2000). Advanced reconstructive methods are sometimes used even when simpler ones are available, if a superior functional result can be achieved.

Free flaps have been shown to withstand RT and chemotherapy well, allowing for uneventfully healed wounds permitting rapid administration of oncological therapy (Peat et al 1994, Disa et al 1997, Evans et al 1997, Kim et al 2004 (A),

Ferguson 2005, Carlson 2006, Tseng et al 2006). The results of this series with only 15% wound complications support these previous findings, and the great majority of patients requiring oncologic treatment were able to begin treatment soon after STS surgery.

The latissimus dorsi flap was by far the most frequently used free flap, utilized in 56% of patients, either as a musculocutaneous or muscle flap. Later in the series, the anterolateral thigh perforator flap was used in 10 patients. Perforator flaps have become popular in breast reconstruction, and are used frequently for reconstructions of both traumatic and oncologic defects in the head and neck as well as in the extremities. Reported advantages of perforator flaps are reduced donor site morbidity and better aesthetic results when thin flaps are required (Geddes et al 2003). Perforator flaps have, however, been criticized for the inconsistent and variable anatomy of the pedicle, the inability to produce functional flaps and for the long learning curve associated with their use (Hallock 2009 (A), Saint-Cyr et al 2009). A major determinant in flap choice after soft tissue sarcoma surgery is, however, the ability of the flap to obliterate dead space and thereby achieve stable, well-healing wounds. Muscle flaps are often better suited for these purposes, as their frequent use in this series shows.

Functional outcome after oncological resection and microvascular reconstruction

Most studies on extremity STS report disease-specific survival rates of 70-80% at five years, corresponding well to survival in studies I-III. As the majority of patients can now be expected to survive for several years after initial operation, functional outcome has become a major determinant of the quality of treatment. It is no longer enough to remove a tumor in an oncologically safe manner, but the surgeon should attempt to achieve optimal functional results. Also, functional results should be quantified during follow-up visits, and reported together with oncological and surgical results. Functional results in this series were generally good, with 75% of lower, and 55% of upper extremity STS patients regaining normal or near-normal function during follow up. A weakness

of this study is the lack of functional scoring and systematic, quantified assessment of functional results. The retrospective nature of the study did not allow such information to be collected. An institution concerned with extremity reconstruction is expected to be able to quantify functional outcome, and the use of one of the several scoring systems (MSTS, TESS etc) would help to increase quality and comparability of results.

Numerous reports on reconstruction of injured collateral ligaments have been published. Reconstruction after resection for malignant disease on the other hand, has been reported in only a few papers. Bickels et al, in a retrospective series on 24 patients, reported good stability in 83% of patients after stapling the lateral collateral ligament to the lateral tibial metaphysis after proximal fibula resection (Bickels et al 2007). Contrary findings were published by Einoder et al, who reported satisfactory outcome in six consecutive patients treated with proximal fibular resection without ligament reconstruction (Einoder et al 2002). No reports on medial collateral ligament reconstruction in oncologic indications have been published to date. Considering the width of resection in the reported cases, instability would have been anticipated in all seven patients with collateral ligament reconstruction. Only one patient did develop instability after medial reconstruction, namely lateral patellar instability. The results should therefore be seen as convincing, but further studies are nonetheless warranted.

After forequarter amputation upper extremity function is lost altogether. Prostheses offer very little functionality, and none of the patients in study IV used an upper extremity prosthesis. Other authors report similar results (Bhagia et al 1997, Clark et al 2003 (A), Daigeler et al 2009). This is not likely to change until better prostheses, offering lighter construction and easier, more versatile operation. Some advances have been made, mainly in the field of targeted reinnervation, which may offer more intuitive prosthesis control (Kuiken et al 2007). At present, considering the cost of individual artificial limb fitting, offering forequarter amputees a shoulder padding for improving shoulder contour may be more recommendable.

Forequarter amputation in oncologic surgery

Results of forequarter amputation in this series further establish this procedure as a valuable alternative in the treatment of upper extremity and shoulder girdle tumors. A DSOS of 44% in the curatively treated group is poor compared to results of studies II and III, but compares well to previous results (Rickelt et al 2009), and must be considered acceptable considering tumor size and difficulty of the cases. In our series, all but one patient (4%) would have agreed to the procedure when asked afterwards. Palliatively treated patients all experienced marked pain relief, indicating that patient selection for palliative FQA is successful. In a series on 45 patients treated with proximal extremity amputations (62% palliative procedures), a subjective increase in quality of life was reported in only 50% of patients, and only 41% of patients would have agreed to the procedure in retrospect. The study also showed that high pain intensity and poor quality of life preoperatively correlated with improved postoperative quality of life (Daigeler et al 2009).

Study IV had no perioperative morbidity, and only 8% wound complications. Free flap success rate was 100%, and there were 17% anastomosis complications. The low wound complication rate can partly be attributed to the cavity filling properties and tension-free closure achieved by liberal use of free flaps. Achieving swift and uneventful recovery is all the more important considering that the majority of palliative forequarter amputees have limited life expectancy, and that the procedure is aimed at improving quality of life.

The results of study IV further show that tumor infiltration into the chest wall is no contraindication to FQA, as the amputation can safely be extended to include chest wall resection. Attention must be paid, however, to reconstructing a stable chest wall allowing effective ventilation (Losken et al 2004). One of the seven patients that underwent FQA and chest wall resection developed respiratory insufficiency in our series. Ver Halen et al reports one perioperative death due to respiratory complications among 16 forequarter amputees (ver Halen et al 2010), and Rickelt et al also reports one death from respiratory failure in their

series on 40 patients that underwent FQA (Rickelt et al 2009). Extended amputation routinely requires reconstructive measures in order to achieve wound closure. A forearm fillet flap from the amputated extremity should be the first choice whenever available. It is a reliable flap with large-caliber vessels for anastomosis, and can be elevated with one or both forearm bones included, to reconstruct the chest wall or contour of the shoulder (Kuhn et al 1994, Osanai et al 2005, ver Halen et al 2010).

Phantom limb pain (PLP) was experienced by 46% of patients in the immediate postoperative period. This corresponds well to earlier reports of 41% PLP after upper extremity amputation (Flor 2002), and 41% PLP in a series of 16 FQA and 7 hemipelvectomy patients (ver Halen et al 2010). Interestingly, PLP was significantly more common in patients with opioid-requiring pain preoperatively, and all patients receiving treatment for neuropathic pain preoperatively did develop PLP. Perioperative epidural pain relief, which has given contradictory results in previous studies (Bach et al 1988, Nikolajsen et al 1997), was not associated with lower rates of PLP in our series. Routine use of perioperative epidural analgesia should perhaps be discontinued until its effect is better documented.

Importance of multidisciplinary management

Multidisciplinary team evaluation should be available for all soft tissue sarcoma patients. Treatment outside a sarcoma center has been shown to increase risk of local recurrence, and by consequence increases morbidity and compromises functional outcome (Mankin et al 1982, Mankin et al 1996, Wiklund et al 1996, Bauer et al 2001, Bhangu et al 2004). Multidisciplinary evaluation allows for optimal planning of diagnostic workup including placement of biopsy tracts so as not to complicate upcoming surgery. Timing and sequencing of surgery can be planned in advance, and delays in administration of oncological treatment can be avoided. In addition, the required plastic surgery expertise should be present, as sufficient width of resection frequently cannot be achieved without reconstructive surgery.

Adherence to sarcoma group protocol in this series was strict, with only 6% of patients being treated in discordance with the protocol. All exceptions to the protocol were based on either individual assessment of the patient, or on patient refusal to undergo treatment. Both surgical and oncological outcome were good even in the challenging patient population requiring microvascular reconstructions after STS surgery, suggesting that the HUCH sarcoma group protocol is well calibrated. The results also indicate that the requirement of a 2.5 cm healthy tissue margin is sufficient. Adherence to the protocol, however, requires readily available reconstructive surgery resources, available in only a few centers in Finland. This supports the view that STS should be treated only at high-volume centers, where sufficient resources and expertise are available.

The centralization of the treatment of STS patients to large sarcoma centers also has the advantage of allowing for centralized follow-up. The median length of follow-up in this series was 61 months, one patient even having been followed up for 224 months at our institution. Up to 7% of STS recurrences take more than 5 years to develop (Zagars et al 2003 (A)), and sufficiently long follow-up protocols are necessary in order to recognize recurrences as early as possible. Also, long periods of reliable follow-up support research, necessary for the continued development of treatment of this challenging group of tumors.

The rarity of soft tissue sarcomas and even greater rarity of individual subtypes makes it difficult for all but the largest sarcoma centers to produce sufficiently large numbers of patients for significant prospective studies to be carried out. The continued quality of sarcoma research depends on close national and international cooperation between sarcoma centers.

10. CONCLUSIONS

I Microvascular reconstruction is a safe and reliable method of reconstructing defects after soft tissue sarcoma surgery near the knee. Reconstruction of collateral ligaments can be performed concurrently with tumor resection, and may increase postoperative knee stability.

II Lower extremity microvascular reconstruction after soft tissue sarcoma resection is safe and reliable. Oncological outcome is excellent. Wound complications are infrequent, and functional results are good.

III Free flap surgery after upper extremity soft tissue sarcoma surgery is an effective and safe method of reconstructing bone and soft tissue defects. Low wound complication rates are achieved, and functional results are satisfactory.

IV Forequarter amputation remains a useful treatment option for malignant tumors of the proximal upper extremity and shoulder girdle. FQA is safe even when extended to include chest wall resection. Curative treatment is possible in selected patients, and considerable intervals of improved quality of life can be achieved for palliatively treated patients. After forequarter amputation, the preferred free flap is a fillet flap from the amputated extremity. It is reliable and versatile, and eliminates the problem of donor site morbidity. The fillet flap provides a solution for soft tissue coverage as well as reconstruction of chest wall stability.

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13. ORIGINAL PUBLICATIONS